Geographic variations in surgical treatment for breast cancer: a systematic review

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Abstract: We conducted a systematic review with the aim of synthesising and examining existing evidence on geographic variations in the type of surgery received for invasive breast cancer. Our focus was on the alternatives of mastectomy or breast conserving surgery followed by radiotherapy. Studies were considered for inclusion if they involved women diagnosed with early invasive breast cancer (stage I-IIIA), were population-based or institution-based, assessed variations in the type of surgical treatment received based on area-level indices such as urban/rural status, accessibility (availability of and proximity to cancer services) and socioeconomic status, and published the findings in English as a full text article. The literature search was carried out from 29 November 2018 to 06 December 2018. Seven electronic databases were systematically searched, 3,109 citations screened, and 40 studies included. The studies were conducted in the United States (US) [31], Canada, China, Japan, and Australia and varied widely in terms of the patient population and geographic measures used. Significant and consistent disparities were found across various geographic locations, with breast conserving surgery being more often received by patients living in urban areas, in areas with better accessibility to cancer care and in areas of higher socioeconomic status. Our findings underscore the need for more efforts to address geographic disparities in breast cancer care. Most studies were from the US, and none from low- or middle-income countries.

Keywords: Breast conserving surgery; mastectomy; geographic variations

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Introduction

Breast cancer is the most common cancer in women worldwide and is also a leading cause of cancer mortality (1). Breast cancer incidence varies internationally with a higher rate observed in Western countries however mortality rates vary less (2). Importantly, geographical inequalities exist within countries at all phases along the cancer care pathway (3-7), which has resulted in survival disparities (4).

Local control is important in breast cancer management as it can influence survival outcomes (8). Historically, mastectomy was the mainstay of primary breast cancer treatment. In the 1980s, several randomised control trials showed comparable survival outcomes for mastectomy and breast conserving therapy (BCT) which consists of breast conserving surgery (BCS) and radiotherapy. Since then, BCT has been established as the preferred modality of surgical treatment as it may lead to less morbidity and a better quality of life (9,10). More recent observational studies reported that survival outcomes were even better for BCT compared to mastectomy (11). Based on these findings, the question is raised of whether women suitable for BCT should still be offered a choice of mastectomy or BCT (9).

Women often choose mastectomy for individual reasons such as fear of cancer recurrence, worry about radiation side-effects, follow-up imaging and recall for further treatment (12). However, broader environmental factors such as travel distance to treatment facilities may also influence treatment decisions (13). This paper therefore aims to review the existing literature on geographic variations in the type of surgery received by women with early invasive breast cancer, focusing on three area-level indices—urban/rural status, accessibility (availability of and proximity to cancer services) and socioeconomic status.

The primary research question for this systematic review was whether the receipt of surgery for invasive breast cancer varies with indicators of access to care. To guide the review, specific secondary questions were: (I) are there urban-rural differences in the receipt and types of surgery for invasive breast cancer? (II) does the proximity and availability of cancer services matter in the receipt of surgery for invasive breast cancer? and (III) are there differences in the receipt and types of surgery for invasive breast cancer by area-level socio-economic status?

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (14) was used to guide the reporting of this review.

Literature Search (information sources; search)

The literature search was carried out between 29 November and 06 December 2018, covering literature from the beginning for each included database till 2018. Searches were conducted across the following databases: Medline [1946–2018], EMBASE [1990–2018], CinhalPlus [1937–2018], Scopus [1970–2018], Cochrane [1992–2018], and Web of Science Core Collection [1900–2018]. Further international literature was sought through the use of WorldWideScience.org. Additionally, further secondary references were assessed for eligibility from the reference lists of publications screened for review.

The keywords and phrases used included *breast cancer*, *breast carcinoma*, *breast tumors*, *rural*, *urban*, *urban-rural difference*, *place of residence*, *regional*, *travel distance*, *geographical or geographic*, *small-area analysis*, *variation*, *disparities*, *radiation therapy*, *surgery*, and *chemotherapy*. The full electronic search strategy conducted on Medline is shown in *Supplementary files*. Note that the search terms used reflect the initial scope and focus of the review which covered all breast cancer treatments.

Eligibility criteria and study selection

Studies were included if they: (I) involved women diagnosed with early invasive breast cancer (stage I-IIIA); (II) were either population-based or institution-based; (III) assessed variations in the type of surgical treatment received based on area-level indices such as urban/rural status, accessibility (availability of and proximity to cancer services) and socioeconomic status, and (IV) published the findings in English as a full text article. Studies that merely reported small-area level or regional/state variations without considering the above-mentioned indices were excluded due to limited generalisability of the results.

All records identified through searched databases and other sources were firstly screened for duplicates. The remaining records were screened for relevance by title and abstract. Then the full text of the remaining articles were retrieved and screened for inclusion in the qualitative synthesis. Additional studies were identified from the references of screened articles. All full-text articles were identified by NC, checked by MSA and approved by STT, JZ and ME to ensure that they met the inclusion criteria and could be included for review.

Data extraction (data collection process and data items)

Data was extracted from each included article using a data collection form, and information on study setting, how the study population was identified and gathered, total patient population, databases/data sources used, area-level indices used, confounding variables controlled for, and main results were collected.

Quality assessment (risk of bias in individual studies and risk of bias across studies)

The quality and risk of bias of each study were assessed using the Newcastle-Ottawa Scale (NOS) for quality assessment of non-randomised studies in meta-analyses (15). The NOS has strong face and content validity and is endorsed by the Cochrane Collaboration. Ratings were made using a point system, where points were given for the selection of study groups; the comparability of the groups; and the assessment of outcomes. The NOS was modified for retrospective cohort studies by omitting the item assessing the presence of the outcome of interest at the beginning of the study. Eight criteria were assessed in the current systematic review: (I) representativeness of the exposed cohort; (II) selection of the non-exposed cohort; (III) ascertainment of exposure; (IV) adjustment for major confounders such as age and stage of diagnosis; (V) adjustment for other possible confounders; (VI) assessment of receipt of surgery; (VII) adequate follow-up period for receipt of surgery; and (VIII) adequacy of follow-up of cohorts. The total quality score was a maximum of eight points with higher scores indicative of higher study quality and less risk of bias.

Presentation of results

Results are presented in four tables, each addressing an indicator of care. The 'results' column gives the results as described in the paper. In addition, a column "key result" expresses that in a consistent fashion, as showing the association between higher use of BCS and urban setting, less distance to facilities, better facilities, and higher socio-economic status. Odds ratios are shown if they are given in the study: for the "key result" their reciprocal may be used.

Results

Study selection

Overall, the search resulted in 3,574 articles identified across Medline, EMBASE, CinhalPlus, Scopus, Cochrane, Web of Science Core Collection, and 783 articles from WorldWideScience.org. After removing duplicates, 3,109 articles remained and were subsequently screened. Seventy-two articles met the inclusion criteria after title and abstract screening. The full-text of these articles were then sought, and 39 were excluded for reasons shown in *Figure 1*. The remaining 33 articles were included in this review with a further 7 studies identified for addition from the reference lists of studies during eligibility screening, making a total of 40 (*Figure 1*).

Study characteristics

Most studies [31] included in this review were from the United States (US), with studies conducted in North Carolina (16), Washington (17), Georgia (18), Kentucky (19-21), Virginia (22-24), Florida (25), South Dakota (26), New Hampshire (27), Michigan (28), and across all regions (29-46). Four other studies were conducted in Canada (47-50), one in China (51), one in Japan (52), and finally, three in Australia (53-55). All were retrospective cohort studies in design. Surgery types examined included the receipt of BCS, BCT, and mastectomy. Further details of the characteristics of the studies are presented in *Tables 1-4*.

Out of the 40 studies, 22 performed analyses at the small area level (e.g., census tract, counties, and cities), 16 at the state level, and two at the national level.

Overall, study quality was good, with many studies [35] receiving quality scores of 7 or 8. The population-based studies were scored 1 for the first criterion (representativeness of the exposed cohort) and institution-based studies were scored 0.5. Most studies used registry and surgical records to examine exposures and outcomes, and controlled for important confounding factors such as age and tumour stage, along with various other factors such as median family income, ethnicity, year of diagnosis, and insurance status.

Results of individual studies

Urban-rural differences

Twenty-three articles examined variations in the receipt of different surgical treatments among women living in urban and rural regions (16,18-22,30,33-36,38,41,42,44,46,48,50-55), and were conducted in the US [16], Australia [3], Canada [2], China [1], and Japan [1] (*Table 1*).

All but one of these studies found that patients living in urban areas were significantly more likely to receive BCS or other more selective surgery, compared to mastectomy, and in the 11 studies where odds ratios are given, the urban excesses were always significant. Only one study (54) found a lower frequency of BCS in an urban area, in Australia, although this was not significant: the study found however that in rural areas radiotherapy was less often used after BCS. The odds ratios reported depend on the categorisations used and may not be comparable: they varied from small variations up to doubling of the odds of receiving BCS in studies in urban areas in Kentucky (20) and in China (51).

Proximity to health care services

Fifteen studies in the US [13] and Canada [2] examined the association between travel distance and the type of surgery received by breast cancer patients (17,22-28,37,39,40,43,45,47,49) (*Table 2*). Fourteen studies found significant differences in the receipt of BCS/BCT versus mastectomy, with women living further away from radiation

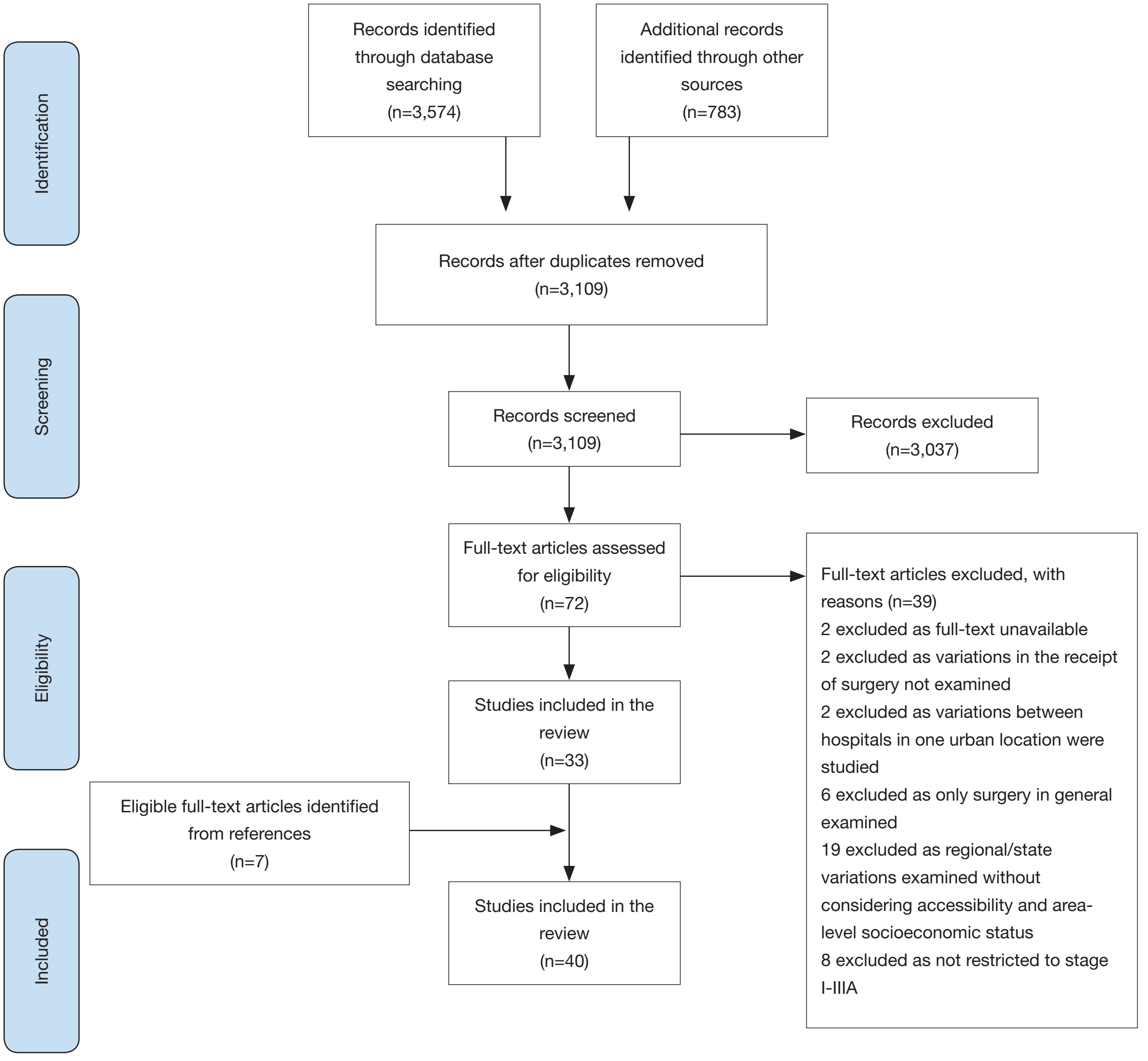

Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram.

treatment facilities and treatment centres less likely to receive BCS and more likely to receive mastectomy (17,23-28,37,39,40,43,45,47,49). Only one study, in Virginia, US, found no significant associations with increasing distance from a treating hospital, but that study did find that large urban hospitals had significantly higher rates of BCT than smaller hospitals (22). However, in a US study of 1,833 women (40) the association was seen for African Americans, in whom it was strong, and no significant association was found in white patients. In one US study, it was initially found that those who lived further away from a radiation therapy facility were more likely to receive mastectomy (24), and when a new radiation facility was opened in the rural area, the rate of mastectomy fell from 61% to 45% among patients who lived within 15 miles of the new facility (24).

Other measures of the availability of health care facilities

Six studies, all conducted in the US, identified variations in the type of breast cancer surgery received by women according to measures other than distance in the availability of health care facilities (22,29,36,41,42,46) (*Table 3*). Most studies showed that women living in areas with more health facilities were more likely to have BCS rather than mastectomy.

Table 1 Variations by urban-rural difference

Author	Study area, country [level of geography]	Patient Identification/ population or Institution	Sample size	Stage	Geographic measures	Type of surgery	Results	Confounders controlled for	NOS Score	Key result: higher BCS in urban: result or OR
Adelson *et al*. [1997] (53)	NSW, Australia [State]	Registry/population	5,040	Local, regional, and metastatic	Regional Health Service (rural regions) *vs*. Area Health Service (urban regions)	Receipt of mastectomy	Adjusted OR for rural regions cf. urban regions =1.561; 95% CI, 1.218–2.001	Age, residence, hospital characteristics, private insurance status, spread of disease	8	Positive 1.56 (1.22–2.00)
Anderson *et al*. [2015] (38)	7 States, United States [Census Tract]	Registry/population	6,505	Stage I-IIIA	Urban *vs*. rural areas	Receipt of BCS *vs*. mastectomy	Adjusted OR for women <65 in rural areas cf. urban areas =0.72; 95% CI, 0.53–0.96; adjusted OR for women ≥65 in rural areas cf. urban areas =0.68; 95% CI, 0.46–1.00	Age at diagnosis, race/ethnicity, health insurance, census tract poverty, census tract education, rural/urban residence, state of residence, surgical facility Commission on Cancer status, clinical tumour stage, tumour size, lymph node status, comorbidity, surgical approach, neoadjuvant chemotherapy	8	Positive 1.39 (1.04–1.89)
Answini *et al*. [2001] (16)	North Carolina, United States [Counties]	Registry/population	3,349	Stage 0-II	Urban *vs*. rural counties	Receipt of BCS	Higher rate of BCS in urban counties than in rural counties		6	Positive
Azzopardi *et al*. [2014] (55)	Australia [Australian Standard Geographical Classification Remoteness Structure]	Clinic/institution	21,643	Stage 0-II	Outer regions *vs*. cities	Receipt of BCS *vs*. mastectomy	Lower rates of BCS and higher rates of mastectomy in outer regions *vs*. cities	Geographic location, tissue diagnosis, surgical treatment, tumour size, histologic grade, number of tumours, lymph node status, lymphovascular invasion	7.5	Positive
Beaulieu *et al*. [2003] (21)	Kentucky, United States [Counties]	Registry/population	8094	Stage I-II	Rural *vs*. urban counties	Receipt of BCS	Lower rates of BCS in rural counties		6	Positive
Craft *et al*. [2010] (54)	Canberra, Australia [State]	Clinic/institution	2,081	Early Breast Cancer	Rural *vs*. metropolitan areas	Receipt of BCS *vs*. mastectomy	Lower in metro area OR 0.82 (0.64–1.07)	Age, residence, tumour size, tumour grade, nodal involvement, hormone receptor status, lymphovascular invasion, type of surgery, place of surgery	7.5	negative, n.s. 0.82 (0.74–1.07)
Dodgion *et al*. [2016] (42)	United States [Census Tract]	Clinic/institution	4,766	Stage 0-IV	Hospitals located in metropolitan *vs*. non-metropolitan areas	Receipt of BCS *vs*. mastectomy *vs*. mastectomy with reconstruction	Lower rates of BCS, higher rates of mastectomy and lower rates of mastectomy with reconstruction at hospitals in non-metropolitan areas	Age, race, census median income, census educational level, tumour stage, nodal stage, oestrogen receptor, progesterone receptor, Her2 neu status, first therapeutic procedure, comorbidity, number of plastic surgeons per 100 annual breast procedures, plastic surgeons per 100,000 female population, radiation oncology services available, mean distance to nearest radiation facility, radiation oncologists per 100,000 female population, total bed size, total number of operating rooms, nursing staff ratio, hospital approval/accreditation, ambulatory surgery, chemotherapy administered, rural urban commuting area code	7.5	Positive
Dragun *et al*. [2012] (19)	Kentucky, United States [Counties]	Registry/population	21,869	Stage 0-II	Rural *vs*. urban counties	Receipt of BCS *vs*. mastectomy	Adjusted OR of receiving mastectomy for rural counties cf. urban counties =1.073; 95% CI, 1.012–1.138	Surgery procedure, race, age at diagnosis, urban/rural status and Appalachian status, year at diagnosis, smoking history, insurance status, survival status at the end of the study, primary cancer sequence number, laterality, stage, nodes examined, ER/PR status, tumour grade, histology, and tumour size	8	1.07 (1.01–1.14)
Elward *et al*. [1998] (22)	Virginia, United States [State]	Clinic/institution	1,512	Stage I-II	Urban hospital *vs*. rural hospital	Receipt of BCS	Higher rates of BCS in large urban hospitals and those with on-campus radiation services	Stage of disease	6.5	Positive
Fisher *et al*. [2015] (50)	Alberta, Canada [State]	Registry/population	14,646	Stage I-III	Rural *vs*. urban regions	Receipt of BCS	Higher rates of BCS in urban centres (Calgary or Edmonton) cf. Central Alberta	Date of diagnosis, age at diagnosis, oestrogen and progesterone receptor status, cancer stage, type of surgery, geographic region of surgery, receipt of neo-adjuvant and adjuvant chemotherapy	8	Positive
Freeman *et al*. [2012] (20)	Appalachian Kentucky, United States [State]	Registry/population	5,541	Stage I-II	Rural *vs*. urban areas	Receipt of mastectomy	Adjusted OR for rural location *vs*. urban location =2.075; 95% CI, 1.743–2.472	Surgery type, race, age at diagnosis, urban/rural status, insurance status, year at diagnosis, smoking status, stage of disease, oestrogen receptor/progesterone receptor status, tumour grade, histology, tumour size, nodes examined	8	2.08 (1.7–2.47)

Table 1 (*continued*)

Table 1 (*continued*)

Author	Study area, country [level of geography]	Patient Identification/ population or Institution	Sample size	Stage	Geographic measures	Type of surgery	Results	Confounders controlled for	NOS score	Key result: higher BCS in urban: result or OR
Gilligan *et al*. [2002] (33)	9 SEER regions, United States [Counties]	Registry/population	158,496	Local and regional	Rural *vs*. urban areas	Receipt of BCT	Lower rates of BCS whether accompanied by RT and LND in rural areas	Age, race, stage of disease, income, education, metropolitan statistical area, SEER site	8	Positive
Haggstrom *et al*. [2005] (34)	SEER Regions, United States [Counties]	Registry/population	22,071	Stage I-II	Rural *vs*. metropolitan areas	Receipt of BCS	Adjusted OR for rural areas cf. metropolitan areas =0.72; 95% CI, 0.65–0.79	Race/ethnicity, age, location of residence, socioeconomic status, individual year of diagnosis, SEER region, tumour size, tumour stage, comorbidity	8	1.58 (1.26–1.97)
Izuo *et al*. [1994] (52)	7 Regions, Japan [State]	Clinic/institution	31,686	Stage I-III	Rural *vs*. cities and urban regions	Receipt of BCS	Lower rates of BCS in rural regions		4.5	Positive
Jacobs *et al*. [2008] (35)	SEER Regions, United States [Counties]	Registry/population	137,303	Stage I-III	Rural *vs*. urban areas	Receipt of mastectomy	Adjusted OR for rural areas cf. urban areas =1.58; 95% CI, 1.26–19.87; adjusted for density per population, and 1.69; 95% CI, 1.38–2.08; adjusted for density per area	Age, race, marital status, income, stage, employment, education, transportation of the study population, density of radiation oncologists, density of radiation technologists	8	1.58 (1.26–1.97)
LeMasters *et al*. [2016] (41)	SEER Regions and West Virginia, United States [Counties]	Registry/population	26,917	Stage I-II	Urban *vs*. rural areas	Receipt of mastectomy and receipt of BCS only *vs*. BCT	Adjusted OR for urban areas cf. rural areas for mastectomy =0.71; 95% CI, 0.65–0.79 Adjusted OR for urban areas cf. rural areas for BCS only *vs*. BCT =0.73; 95% CI, 0.75–0.8	Initial local treatment, year of diagnosis, age, frequency of Primary Care Provider visits, stage at diagnosis, ER status, PR status, tumour grade, area-level density of mammography screening and oncology treatment centres, specialisation of the treating surgeon(s), race, education, annual income, metro status	8	1.41 (1.54–1.27)
Liu *et al*. [2012] (51)	Tianjin, China [City]	Clinic/institution	468	Stage I-II	Urban *vs*. rural areas	Receipt of BCT	Adjusted OR for urban areas cf. rural areas =2.14; 95% CI, 1.29–3.56	Age, educational level, occupation, family income, medical insurance, residence, source of BCT information, communication with the attending physician, tumour location, clinical stage, pathology, lymph node involvement, oestrogen receptor status	7.5	2.14 (1.29–3.56)
Markossian *et al*. [2012] (18)	Georgia, United States [Counties]	Registry/population	23,500	Stage 0-IV	Rural *vs*. urban areas	Receipt of BCS	Adjusted OR for rural areas cf. urban areas =0.73; 95% CI, 0.58–0.91	Age at diagnosis, race, hormone receptor status, tumour characteristics, county of residence, AJCC stage, hormone receptor status, tumour grade, BC treatment, surgery type, county-level SES, survival status	8	1.37 (1.72–1.10)
Michalski, *et al*. [1997] (30)	United States [Census Tract]	Registry/population	41,937	Stage I-III	Urban areas *vs*. rural areas	Receipt of BCS	Significant negative association with increasing rurality	Socioeconomic factors (median family income, mean proportion of college graduates, mean proportion of the population living below the poverty line, mean proportion of vacant housing units), race, stage of disease, population size of the zip code	8	Positive
Nattinger, *et al*. [1992] (44)	United States [National]	Registry/population	36,982	Stage I-III	Non-metropolitan areas *vs*. metropolitan areas	Receipt of BCS	Significant positive association with increasing size of metropolitan areas	Race; population of metropolitan area, full-time house staff, geriatric services, radiation therapy facility	7	Positive
Samet *et al*. [1994] (46)	9 SEER Regions, United States [Counties]	Registry/population	19,661	Stage I-III	City of ≥10,000 in county	Receipt of BCS	Adjusted OR for city of ≥10,000 in county cf. city of <10,000 in county =1.18; 95% CI, 1.10–1.28	Age at diagnosis, SEER region, number of physicians per 10,000 residents, percentage of residents with 16 or more years of education, percentage of families with incomes below the poverty level, presence of a city of 100,000 or larger within the county, and presence of a cancer treatment centre within the county, race	8	1.18 (1.10–1.28)
Smith *et al*. [2009] (36)	United States [Counties]	Registry/population	56,725	Stage I-II	Metropolitan areas *vs*. non-metropolitan areas	Receipt of BCS	Higher rates of BCS in metropolitan areas cf. non-metropolitan areas	Age, race, comorbidity score, axillary lymph node involvement, axillary dissection, chemotherapy, screening mammography, physician visits, surgeon density, radiation oncologist density, metropolitan area, education, tumour stage	8	Positive

"Key result" column positive means a higher BCS rate in urban areas, or the odds ratio and 95% limits for this association, if given. This is sometimes the reciprocal of that given in the paper. BCS, breast conserving surgery; BCT, breast conserving therapy; RT, radiotherapy; LND, lymph node dissection.

Table 2 Variations by cancer care accessibility (proximity to services)

Author	Study area, country [level of geography]	Patient identification/ population or institution	Sample size	Stage	Geographic measures	Type of surgery	Results	Confounders controlled for	NOS Score	Key result: more BCS if closer
Baldwin *et al*. [2004] (17)	Washington, United States [State]	Registry/population	1,188	Local and regional	Distance from the radiation therapy centre	Receipt of BCS and radiotherapy *vs*. mastectomy	Adjusted OR for women living ≥40 miles cf. women living <30 miles from radiotherapy centre =0.62 [P=0.10]; >50 miles cf. women living <30 miles =0.58 [P=0.09]	Preoperative radiation and medical oncology consultation, surgical procedure, age at diagnosis, ethnicity, marital status, median household income, disease stage at diagnosis, tobacco use, case severity, rural or urban residence, residence in nursing home	8	Positive: OR 1.61, n.s.
Boscoe *et al*. [2011] (45)	10 States, United States [State]	Registry/population	104,730	Early stage breast cancer	Distance to surgery proximity	Receipt of mastectomy	Significant positive associations with surgery proximity	Age, year of diagnosis, race, ethnicity, census tract-level household poverty rate and rural/urban status, tumour sequence, commuting proximity	8	Positive
Celaya *et al*. [2006] (27)	New Hampshire, United States [State]	Registry/population	2,861	Stage I-IIB	Distance to a radiation treatment facility	Receipt of BCS and radiotherapy	Significant negative associations with distance to a radiation treatment facility	Age at diagnosis, marital status, primary sequence, distance to radiation treatment facility, time of year, tumour size, stage at diagnosis	8	Positive
Elward *et al*. [1998] (22)	Virginia, United States [State]	Clinic/institution	1,512	Stage I-II	Distance from the treating hospital	Receipt of BCS	No significant associations with distance from the treating hospital	Stage of disease	6.5	No association
Greenberg *et al*. [2011] (37)	8 States, United States [State]	Clinic/institution	10,607	Stage I-II	Distance to radiation facility	Receipt of BCS *vs*. mastectomy with reconstruction	Significant positive associations of mastectomy with reconstruction, compared to BCS with increasing distance to radiation facility. OR per mile, 1.03 (1.00–1.05)	Age, systemic treatment, BMI, comorbidity score, income level, tumour size, number of positive nodes, HR status, AJCC stage, type of health insurance at presentation, employment status, number of reconstructive surgeons at each NCCN site, number of radiation oncologists on staff treating breast cancer at the beginning at each site	7.5	Positive
Hislop *et al*. [1996] (47)	British Columbia, Canada [Census Tract]	Registry/population	942	Stage I-II	Distance to radiation treatment facility	Receipt of BCS	Significant negative association. Adjusted OR for <2 hours drive cf. 2+ hour drive =0.56; 95% CI, 0.36–0.76	Age at diagnosis, place of residence, median family income of neighbourhood, tumour size, histological type, tumour location in the breast, extent of ductal carcinoma in-situ, surgeon's sex, caseload, graduation year from medical school, university affiliation, family physician's graduation year from medical school and university affiliation	8	Positive 1.79 (1.32–2.78)
Lautner *et al*. [2015] (39)	United States [national]	Registry/population	727,927	Stage I-IIIA	Distance to a treatment facility	Receipt of BCT	Adjusted OR for patients with a travel distance of less than 27.7 km =1.21; 95% CI, 1.16–1.26	Year of breast cancer diagnosis; age; race/ethnicity; comorbidity; insurance status; median income; population without high school diploma; facility type; facility location; distance from treatment facility; clinical T stage; clinical N stage; hormone receptor status	8	Positive: 1.21 (1.16-1.26)
Lin *et al*. [2018] (26)	South Dakota, United States [Census Tract]	Registry/population	4,031	Stage I-II	Distance from a radiation therapy facility	Receipt of mastectomy	Significant positive association with distance to radiation therapy facility	Race/ethnicity, age at diagnosis, tumour grade, tumour sequence, year of diagnosis, poverty rate, urban/rural residence, travel distance to closest radiation therapy facility	8	Positive
Mandelblatt *et al*. [2002] (40)	United States [Census Tract]	Registry/population	1,833	Stage I-II	Distance from nearest cancer centre	Receipt of mastectomy *vs*. BCT	For African-American patients, significant positive association. Adjusted OR for fourth quartile cf. first quartile =3.13; 95% CI, 1.22–8.08 No significant association for white patients	Surgical treatment received, chemotherapy, tamoxifen race, age, comorbidity, stage, area percent of elderly below poverty, area percent of HS education, individual monthly income, individual education, marital status, supplemental insurance, mean urban-rural continuum score, mean number of radiology specialists per 100,000, mean number of surgeons per 100,000, median distance to cancer centre, region perceptions of racism and ageism	8	Positive: 3.13 (1.22–8.08) (Af-Amer) Np association (white)
Meden *et al*. [2002] (28)	Michigan, United States [State]	Clinic/institution	66	Stage I-II	Travel distance to radiation oncology facility	Receipt of BCT	Significant negative association with distance to a radiation oncology facility		5.5	Positive
Nattinger *et al*. [2001] (43)	SEER Regions, United States [Census Tract]	Registry/population	17,729	Stage I-II	Distance from a radiation therapy facility	Receipt of BCS	Significant negative association with increasing distance from a radiation therapy facility	Age, stage of disease, race, education status, distance to hospital with radiotherapy facility, population density, SEER site	8	Positive
Parviz *et al*. [2003] (23)	Virginia, United States [State]	Clinic/institution	928	Stage 0-II	Distance from a radiation centre	Receipt of BCT	Adjusted OR for distance of >40 miles away from a radiation centre cf. distance of <40 miles away from a radiation centre =0.48; P=0.007	Age, race, insurance status, stage, year of diagnosis, treating surgeon, type of surgery	7.5	Positive, OR =2.08
Schroen *et al*. [2005] (24)	Virginia, United States [State]	Registry/population	20,094	Stage I-III	Distance from nearest radiation facility	Receipt of mastectomy	Significant positive association with increasing distance from nearest radiation facility	Age, race, year of diagnosis, tumour extent of disease, tumour size, distance to nearest RT facility	8	Positive
Voti *et al*. [2006] (25)	Florida, United States [Census Tract]	Registry/population	18,903	Stage I-IIA	Distance from the closest radiation therapy facility	Receipt of BCT	Significant negative association with increasing distance from the closest radiation therapy facility	Age at diagnosis, distance to radiation therapy facilities, marital status, insurance at the time of diagnosis, race/ethnicity	8	Positive
Xu *et al*. [2018] (49)	Alberta, Canada [State]	Registry/population	21,872	Stage 0-III	Distance to the nearest radiotherapy centre	Receipt of mastectomy	Significant positive association with increasing distance to the nearest radiotherapy centre. However, association not significant for Calgary and Red Deer regions	Primary surgery type, region, driving time, period of diagnosis, age, AJCC stage, RT centre, adjuvant therapy, tumour size, lobular histology type, lymph node involvement, tumour grade, molecular subtype, comorbidities, surgical institution type, educational attainment of neighbourhood, neighbourhood annual income, re-excision, chemotherapy use, anti-endocrine use, radiotherapy use	8	Positive

"Key result" column positive means a higher BCS rate with a lower distance to facilities, or the odds ratio and 95% limits for this association, if given. This is sometimes the reciprocal of that given in the paper. BCS, breast conserving surgery; BCT, breast conserving therapy; RT, radiotherapy.

Table 3 Variations by cancer care accessibility (availability of services)

Author	Study area, country [level of geography]	Patient Identification/ population or institution	Sample size	Stage	Geographic measures	Type of surgery	Results	Confounders controlled for	NOS score	Key result: higher BCS if more access
Ballard-Barbash *et al*. [1996] (29)	9 SEER Regions, United States [Census Tract]	Registry/population	18,704	Stage I-IIB	Number of physicians and hospitals with radiation megavolt equipment in the area	Receipt of BCS	Adjusted OR for areas with 801-930 physicians per 10,000 population =1.32, 95% CI, 1.16–1.50 cf. areas with >930 physicians per 10,000 population	Age, stage of disease at diagnosis, ethnicity, comorbidity, health care characteristics, region	8	Negative: OR 0.76 (0.67–0.86)
							Adjusted OR for areas with >8 hospitals with radiation therapy megavolt units cf. areas with <3 hospitals with radiation therapy megavolt units =1.35, 95% CI, 1.21–1.51			Positive: 1.35 (1.21–1.51)
Dodgion *et al*. [2016] (42)	United States [Census Tract]	Clinic/institution	4,766	Stage 0-IV	Availability of radiation oncology services within the hospital or network	Receipt of BCS *vs*. mastectomy *vs*. mastectomy with reconstruction	Lower rates of BCS, higher rates of mastectomy and lower rates of mastectomy with reconstruction with lack of availability of radiation oncology services within the hospital or networks	Age, race, census median income, census educational level, tumour stage, nodal stage, oestrogen receptor, progesterone receptor, Her2 neu status, first therapeutic procedure, comorbidity, number of plastic surgeons per 100 annual breast procedures, plastic surgeons per 100,000 female population, radiation oncology services available, mean distance to nearest radiation facility, radiation oncologists per 100,000 female population, total bed size, total number of operating rooms, nursing staff ratio, hospital approval/accreditation, ambulatory surgery, chemotherapy administered, rural urban commuting area code	7.5	Positive
Elward *et al*. [1998] (22)	Virginia, United States [State]	Clinic/institution	1,512	Stage I-II	Presence of senior	Receipt of BCS	Higher rates of BCS in the presence of Senior Membership Programs and Women's Health Centres in the community	Stage of disease	6.5	Positive
					Members Hip Programmes and Women's Health Centres in the community		Higher rates of BCS in large urban hospitals and those with on-campus radiation services			Positive
					Type of hospital		Similar rates of BCS in hospitals that reported availability of these services through referral or transport *vs*. those without available services			No association
LeMasters *et al*. [2016] (41)	SEER Regions and West Virginia, United States [Counties]	Registry/population	26,917	Stage I-II	Density of mammography and oncology treatment centres	Receipt of mastectomy *vs*. BCT	Adjusted OR for areas with high density of mammography screening centres cf. areas with low density, for mast *vs*. BCT =0.98, 95% CI, 0.86–1.12	Initial local treatment, year of diagnosis, age, frequency of Primary Care Provider visits, stage at diagnosis, ER status, PR status, tumour grade, area-level density of mammography screening and oncology treatment centres, specialisation of the treating surgeon(s), race, education, annual income, metro status	8	No association: 1.02 (0.89–1.16)
							Adjusted OR for areas with high density of oncology treatment centres cf. areas with low density for mastectomy *vs*. BCT =0.87, 95% CI, 0.76–0.99			Positive: 1.15 (1.01–1.32)
Samet *et al*. [1994] (46)	9 SEER Regions, United States [Counties]	Registry/population	19,661	Stage I-III	Physician-to-population ratio	Receipt of BCS	Adjusted OR for 26.3 or more physicians per 10,000 cf. fewer than 16.5 per 10,000=1.40, 95% CI 1.27–1.53	Age at diagnosis, SEER region, number of physicians per 10,000 residents, percentage of residents with 16 or more years of education, percentage of families with incomes below the poverty level, presence of a city of 100,000 or larger within the county, and presence of a cancer treatment centre within the county, race	8	Positive: 1.40 (1.27–1.53)
					Presence of a cancer centre		Adjusted OR for cancer centre in county cf. no cancer centre in county =1.24, 95% CI, 1.12–1.37			Positive: 1.24 (1.12–1.37)
Smith *et al*. [2009] (36)	United States [Counties]	Registry/population	56,725	Stage I-II	Density of radiation oncologists	Receipt of BCS	Adjusted OR for higher density of radiation oncologists cf. lower density of radiation oncologists =1.37, 95% CI, 1.07–1.75	Age, race, comorbidity score, axillary lymph node involvement, axillary dissection, chemotherapy, screening mammography, physician visits, surgeon density, radiation oncologist density, metropolitan area, education, tumour stage	8	Positive: 1.37 (1.07–1.75)

BCS, breast conserving surgery; BCT, breast conserving therapy; RT, radiotherapy. "Key result" column positive means a higher BCS rate with better access, or the odds ratio and 95% limits for this association, if given. This is sometimes the reciprocal of that given in the paper.

Thus, higher rates of BCS were seen in areas with a high density of radiation oncologists and a greater number of physicians (36,46), areas with a cancer care centre (46), and a high density of oncology treatment centres (41). Similarly, older patients who lived in areas with the presence of Senior Membership Programmes and Women's Health Centres had higher rates of BCS (22). Areas with less availability of radiation oncology services within hospitals or hospital networks had higher rates of mastectomy and lower rates of mastectomy with reconstruction (42). Women from areas with a greater number of hospitals with radiation therapy megavolt equipment were more likely to receive BCS (29). Only a few findings were inconsistent: in this last study (29), women were more likely to receive BCS if they were in areas with a lower rate of physicians per 10,000 population. One study (41) also found that women in areas with a higher density of mammography screening centres are more likely to receive RT after BCS (41).

Area level socioeconomic status

Eleven studies, 10 in the US and one in Canada, examined and identified differences in the type of surgery received by breast cancer patients residing in areas of different socioeconomic status (26,29-34,38,40,46,48) (*Table 4*). All 11 studies found that women living in higher socioeconomic areas were more likely to receive BCS. In areas with a greater proportion of college graduates and higher education levels, patients were significantly more likely to receive BCS/BCT than mastectomy (29-31,33,38,46). Similarly, patients living in areas with a higher median income were more likely to receive BCS (30-34). Conversely, patients living in areas with a greater proportion of people living below the poverty line and in areas with lower median incomes were less likely to receive BCS and were significantly more likely to receive a mastectomy (26,30,32,33,40,46,48).

Discussion

This systematic review found that significant geographic variations existed in the receipt of different types of surgery in women diagnosed with early breast cancer. The evidence was generally consistent across the US as well as in the few studies from Canada, Australia, China, and Japan.

To our knowledge, this is the first systematic review on geographic variations assessed by area-level indicators in the types of surgery received by breast cancer patients. The review was limited to articles published in English only. As the majority of studies were published in the US (31 out of 40 studies included for review), the generalisability of our results may be limited as the healthcare systems are vastly different across countries, both in terms of funding and structure. As this review was based on peer-reviewed studies, we did not consider grey literature such as cancer registry reports or studies based on individual level data. We also excluded the studies that reported geographic differences only within a small area. We used the NOS scale to assess quality; this may not be sufficiently discriminating, as most studies received a high score. Several studies showed the size of these differences by odds ratios, which generally suggested variations of 20–50%, but the odds ratios were not comparable as they depended on the categorisation of the factors considered. Therefore, we do not present a quantitative meta-analysis.

We identified geographic variations in surgery types, in terms of urban and rural settings, distance and other aspects of accessibility to cancer care, and area-level socio-economic status. In general, women living in urban areas, in close proximity to cancer care facilities, particularly radiation centres, and in more affluent neighbourhoods were more likely to receive BCS, and less likely to receive mastectomy. Similar findings have been reported in other narrative reviews on this topic (3,6,56). Ayanian *et al.* reported that patients living in urban and metropolitan areas were more likely to receive BCS than patients living in rural areas, with the likelihood of receipt of BCS being strongly associated with the size of the metropolitan region (6). Two other reviews also found that breast cancer patients were less likely to receive BCS if they had greater travel distance from cancer treatment centres and radiotherapy facilities (3,56). Other reviews have identified geographic disparities across the breast cancer care continuum, from diagnosis to survival (4,6,7,56). Overall, the evidence to date shows that area of residence and accessibility to cancer care play an important role in the types of cancer treatment received by breast cancer patients.

Our review of peer-reviewed literature showed that most studies were from the US. The US health care system has greater disparities in access to care than other developed countries (57). The few studies from other countries suggest their situation may be different. The only study not showing an urban-rural difference was from Australia (54), although the other Australian study did show an urban effect (53); in Ontario, Canada, differences were non-significant (48), although urban increases in BCS were seen in British Columbia and in Alberta (48,50). However,

Table 4 Variations by area-level socioeconomic status

Author	Study area, country [level of geography]	Patient identification/ population or institution	Sample size	Stage	Geographic measures	Type of surgery	Results	Confounders controlled for	NOS Score	Key result: more BCS if SES higher
Anderson *et al.* [2015] (38)	7 States, United States [Census Tract]	Registry/population	6,505	Stage I-IIIA	Census tract education	Receipt of BCS *vs.* mastectomy	Adjusted OR for women <65 years in areas with high census tract education cf. areas with low census tract education =1.20, 95% CI, 0.93–1.54 Adjusted OR for women ≥65 years in areas with high census tract education cf. areas with low census tract education =1.54, 95% CI, 1.09–2.16	Age at diagnosis, race/ethnicity, health insurance, census tract poverty, census tract education, rural/urban residence, state of residence, surgical facility Commission on Cancer status, clinical tumour stage, tumour size, lymph node status, comorbidity, surgical approach, neoadjuvant chemotherapy	8	Positive
Ballard-Barbash *et al.* [1996] (29)	9 SEER Regions, United States [Census Tract]	Registry/population	18,704	Stage I-IIB	Census tract education	Receipt of BCS	Adjusted OR for census tracts with high education levels cf. census tracts with low education levels =1.15, 95% CI, 1.05–1.28	Age, stage of disease at diagnosis, ethnicity, comorbidity, health care characteristics, region	8	Positive
Gilligan *et al.* [2002] (33)	9 SEER Regions, United States [Counties]	Registry/population	158,496	Local and regional	County income County education	Receipt of BCT	Lower rates of BCS whether accompanied by RT and LND in poorer counties Higher rates of BCT accompanied by RT and LND in better educated counties No significant association if RT, LND or both omitted	Age, race, stage of disease, income, education, metropolitan statistical area, SEER site	8	Positive
Goel *et al.* [1997] (48)	British Columbia and Ontario, Canada [State]	Registry/population	942	Node-negative breast cancer	Area median income level	Receipt of BCS	Lower rates of BCS in areas with lower median incomes. However, only significant in British Columbia	Age, tumour size and location	8	Positive
Haggstrom *et al.* [2005] (34)	SEER Regions, United States [Counties]	Registry/population	22,071	Stage I-II	Area socioeconomic status	Receipt of BCS	Significant positive association with increasing area socioeconomic status	Race/ethnicity, age, location of residence, socioeconomic status, individual year of diagnosis, SEER region, tumour size, tumour stage, comorbidity	8	Positive
Lin *et al.* [2018] (26)	South Dakota, United States [Census Tract]	Registry/population	4,031	Stage I-II	Census tract federal poverty line	Receipt of mastectomy	Adjusted OR for census tracts with greater than 15% of the population under the federal poverty line cf. census tracts with less than 5% of the population under the federal poverty line =1.28, 95% CI, 1.02–1.61	Race/ethnicity, age at diagnosis, tumour grade, tumour sequence, year of diagnosis, poverty rate, urban/rural residence, travel distance to closest radiation therapy facility	8	Positive
Mandelblatt *et al.* [2002] (40)	United States [Census Tract]	Registry/population	1,833	Stage I-II	Area percent of elderly below poverty level quartiles	Receipt of mastectomy *vs.* BCT	Adjusted OR for areas highest quartile of elderly residents living below poverty level cf. lowest quartile of poverty =7.59, 95% CI, 2.81–20.5	Surgical treatment received, chemotherapy, tamoxifen race, age, comorbidity, stage, area percent of elderly below poverty, area percent of HS education, individual monthly income, individual education, marital status, supplemental insurance, mean urban-rural continuum score, mean number of radiology specialists per 100,000, mean number of surgeons per 100,000, median distance to cancer centre, region perceptions of racism and ageism	8	Positive
McGinnis, *et al.* [2000] (32)	United States [State]	Registry/population	191,714	Stage I-III	Zip code income level	Receipt of mastectomy	Higher rates of partial mastectomy with or without radiation or systemic therapy in higher income zip codes Higher rates of modified radical mastectomy in lower income zip codes	Stage of disease, race	8	Positive
Michalski *et al.* [1997] (30)	United States [Census Tract]	Registry/population	41,937	Stage I-III	Area median family income	Receipt of BCS	Adjusted OR for areas with highest median family income cf. areas with lowest median family income =1.1, 95% CI, 1.0–1.2	Socioeconomic factors (median family income, mean proportion of college graduates, mean proportion of the population living below the poverty line, mean proportion of vacant housing units), race, stage of disease, population size of the zip code	8	Positive
					Area percentage of college graduates		Adjusted OR for areas with the greatest percentage of college graduates cf. areas with the lowest percentage of college graduates =1.2, 95% CI, 1.1–1.4			Positive
					Area proportion of persons living below the poverty level		Adjusted OR for areas with the greatest proportion of persons living below the poverty line =0.8, 95% CI, 0.7–0.9			Positive
Riley *et al.* [1999] (31)	United States [Census Tract]	Registry/population	28,608	Stage I-IIB	Area education level	Receipt of BCS	Adjusted OR for areas with lowest quartile education level cf. areas with highest quartile education level =0.80, 95% CI, 0.73–0.87	Age, race, state and county of residence, cancer history, year of diagnosis, percentage of adults with fewer than 12 years of education at the census tract level, stage at diagnosis, tumour size, treatment pattern	8	Positive
Samet *et al.* [1994] (46)	9 SEER Regions, United States [Counties]	Registry/population	19,661	Stage I-III	Percent of county with college education	Receipt of BCS	Adjusted OR for areas with 24.0 or more percent of county with college education cf. areas with less than 16.5% of county with college education =1.68, 95% CI, 1.53–1.85	Age at diagnosis, SEER region, number of physicians per 10,000 residents, percentage of residents with 16 or more years of education, percentage of families with incomes below the poverty level, presence of a city of 100,000 or larger within the county, and presence of a cancer treatment centre within the county, race	8	Positive
					Percent of county below poverty level		Adjusted OR for areas with 8.6 or more percent of county under poverty level cf. less than 6.1 percent of county below poverty level =0.72, 95% CI, 0.66–0.78			Positive

"Key result" column positive means a higher BCS rate with higher socio-economic status, or the odds ratio and 95% limits for this association, if given. This is sometimes the reciprocal of that given in the paper. BCS, breast conserving surgery; BCT, breast conserving therapy; RT, radiotherapy; LND, lymph node dissection.

higher rates of BCS were seen in higher socio-economic groups in British Columbia, as in the several US studies (48). In a related study, women in the lowest socio-economic groups in Ontario and in California were compared, and the Ontario women were more likely to receive BCS (58); this study was not included as it did not give results comparing different socio-economic groups within either area. Our review found no studies from Europe; perhaps the question is regarded as unimportant there, or studies were published only in grey literature or non-English language journals. There are also no studies from low or middle-income countries. It would be valuable to have more information from other countries; specifically, studies of health systems in which these variations in care may potentially not occur would be useful.

The provision of BCS plus RT as an alternative to mastectomy requires a more comprehensive and costly service. A surgeon working alone or in a small practice can provide mastectomy. To give BCS plus RT requires a team approach including a radiotherapist, RT facilities, and extended care over several weeks. Thus, the indicators of urban residence and closeness to large facilities or to more sophisticated services used in these studies likely all relate to whether the women gets her care at a facility offering a true choice of treatments. The other key issue is patient choice, and distance from facilities and socio-economic status are probably indicators of the patient's ability to accept the weeks of regular RT and cope with the demands on her family and work commitments and the costs (59). The other key influence on choice of treatment is how the options are viewed by the doctors involved and by the patient, and how that discussion is framed and how the decision is made (59). The use of BCS rather than mastectomy has been used sometimes as a clinical care quality indicator, but ideally patient choice and shared decision-making should be also considered (59,60).

Geographical variations and specifically urban-rural differences in care provision are a major challenge for all governments worldwide, and are a priority in cancer control plans and service provision. For example, in 2019 the American Society for Clinical Oncology announced a new task force to address the "rural cancer care gap" in the US (61). Inequities related to access to care exist in participation in screening programs, stage distribution and late diagnosis, and the use of most types of treatment. Radiotherapy is the most difficult treatment to provide equitably, as it requires expensive equipment, dedicated premises, and a specialised workforce. It is inevitable that many patients will live far from the nearest radiotherapy centre. The national radiotherapy plan for England proposes that all patients should live within 45 min travel time to their nearest centre, and so new satellite centres have been developed (62). Surgical services are more widely distributed, but quality varies, and there is good evidence that surgeons with higher cancer workloads give better outcomes (63), so access to the best service may be difficult. In Australia, BCS was less frequently used by women whose surgeons have a low case load, independently of the effect of rural residence (64). In northern Italy, lower use of BCS was seen in women treated at hospitals with low surgical volumes, as well as in those living far from radiotherapy facilities (65). Chemotherapy services can be provided locally if there is a system of training specialised nurses, and ensuring protocols used in the main centres are followed. Systems of giving primary care physicians extra training to enable them to supervise such services can be beneficial. Such a program exists in British Columbia, Canada, where rural patients were less likely to have BCS, but did not have reduced chemotherapy or hormonal therapy (66). Even primary care services for cancer have difficulties, and education and support for rural practitioners can be beneficial (67).

It seems likely that variations in the type of breast surgery used are largely driven by the requirement for radiotherapy after BCS and hence the issues of access to radiotherapy, which normally requires multiple visits over many weeks. New developments such as intra-operative radiotherapy, where radiotherapy is given only at the time of surgery, could improve access, but may be only appropriate for selected patients (68). It is understandable that women in rural areas more often opt to have mastectomy, thus avoiding the need for radiotherapy. However, the size of this variation may seem surprising. In Queensland, the use of BCS in very low access areas was less than half of that in the best access areas (13). In a study in 10 states in the US, the use of BCS was reduced by 30% in women living more than 75 km from a radiotherapy centre (45), with similar findings in South Dakota; but in New Jersey, similar disparities were seen in those living more than 15 km or 19 min travel time away (69). Distance from the centres relates to travel time, cost, and inconvenience. In New Hampshire, a northern US state with severe winters, the use of BCS was lower with greater travel time, and also lower in winter. In Northern England, the use of BCS was not related to travel time in general, but was lower for women living in areas with no regular bus service (70).

It would be expected that variations in treatment by distance would be more marked for less affluent patients, in terms of direct cost, but also in terms of difficulties in employment and childcare. Few studies have appeared to look at this interaction, but several have reported lower BCS use in the lower socio-economic groups. In Florida, a reduction in BCS with increasing distance was seen in older women, but not in those under 50 years (71).

While these access issues have been well described, there seem to have been few interventions to improve them. In one area of New South Wales, the use of BCS showed no change after a free transport service to the nearest radiotherapy facilities (68 and 86 km distant) was introduced, but increased significantly when a local free radiotherapy service was started, with the largest increase for patients over age 70 (72).

Conclusions

This systematic review found that for women with early invasive breast cancer, higher rates of breast-conserving surgery rather than mastectomy were consistently associated with urban location, closeness to facilities, more advanced facilities, and higher socio-economic status. These variations were seen in many studies from the US, several having good control for clinical factors such as stage of disease, although our review did not address patient choice. Our findings highlighted that inequalities in care exist which may be substantial. The lack of studies from countries other than the US limits the ability to understand the extent of inequalities in other countries. There are no studies from low- or middle-income countries. Variations in care given, if not for clinical reasons or for informed patient choice, need to be documented and addressed in cancer care planning.

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Supplementary

Medline (1946-2018) - 455 studies/articles identified

1. Search terms used
1. Breast cancer.mp.
2. Breast carcinoma.mp.
3. Breast neoplasm*.mp.
4. Breast Neoplasms/
5. Breast tumor*.mp.
6. Breast tumour.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Rural.mp.
9. Urban.mp.
10. Urban-rural difference*.mp.
11. Metropolitan.mp.
12. suburb*.mp.
13. District.mp.
14. remote*.mp.
15. Remote population.mp.
16. Location.mp.
17. Geographic.mp.
18. Geographic pattern.mp.
19. Geographic loca*.mp.
20. Region.mp.
21. Spatial analysis/
22. Spatial analys*.mp.
23. Place of residency.mp.
24. Place of residence.mp.
25. Rural Population/
26. Rural population.mp.
27. Urban population/
28. Urban population.mp.
29. Rural health/
30. Rural health services/
31. Hospitals, rural/
32. Urban health/
33. Hospitals, urban/
34. Travel distance.mp.
35. Travel time.mp.
36. Travel burden.mp.
37. Health service access*.mp.
38. Healthcare access*.mp.
39. Health service* accessibility.mp.
40. Health services accessibility/
41. Availability.mp.
42. Distance.mp.
43. utili#ation.mp.
44. Health service utili#ation.mp.
45. Geographic information system*.mp.
46. Geographic information systems/
47. Geospatial analysis.mp.
48. Geospatial analyses.mp.
49. Geographic mapping/
50. Small-area analysis/
51. Small area.mp.
52. Small area analys#s.mp.
53. Cancer map.mp.
54. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. variation*.mp.
56. Disparity.mp.
57. Disparities.mp.
58. Healthcare Disparities/
59. Health care disparities.mp.
60. Inequality.mp.
61. Inequalities.mp.
62. difference*.mp.
63. Distribution.mp.
64. Disadvantage.mp.
65. 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64
66. radiotherapy/
67. Radiotherapy.mp.
68. Drug Therapy/
69. chemotherap*.mp.
70. Systemic treatment*.mp.
71. Systemic therapy.mp.
72. Systemic therapies.mp.
73. Local treatment*.mp.
74. Local therapy.mp.
75. Local therapies.mp.
76. hormon* therapy.mp.
77. hormon* therapies.mp.
78. Locoregional treatment*.mp.
79. Breast cancer surgery.mp.
80. Mastectomy/
81. Mastectomy.mp.
82. Breast conserving surgery.mp.
83. Mastectomy, Segmental/
84. Lumpectomy.mp.
85. Axillary surgery.mp.
86. General Surgery/
87. Surgery.mp.
88. Biological treatment*.mp.
89. Targeted therapy.mp.
90. Targeted therapies.mp.

91. Treatment.mp.
92. 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91
93. Receipt.mp.
94. Receiving.mp.
95. Compliance.mp.
96. Patient Compliance/
97. "Treatment Adherence and Compliance"/
98. 93 or 94 or 95 or 96 or 97/
99. 7 and 54 and 65 and 92 and 98